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MULTILYTE LTD.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

AFFYMETRIX, INC., a Delaware corporation,

Plaintiff and Counterdefendant,

v.

MULTILYTE LTD., a British corporation,

Defendant and Counterclaimant.

Case No.: C-03-3779 WHA

DECLARATION OF DR. LARRY J. KRICKA IN SUPPORT OF MULTILYTE LTD.'S OPENING CLAIM CONSTRUCTION BRIEF

I, Larry J. Kricka, declare:

1. I submit this declaration in support of Multilyte Ltd's Opening Claim Construction Brief. In particular, I have been asked to provide opinions regarding the construction of certain terms as used in U.S. Patent No. 5,559,720 ("the '720 patent"); U.S. Patent No. 5,432,099 ("the '099 patent"); and/or U.S. Patent No. 5,807,755 ("the '755 patent"). This declaration summarizes my opinions on these issues.

Educational Background and Experience

2. I hold a D. Phil. degree in Chemistry from York University, England, and I have a B.A. degree, with honors, in Chemistry, also from York University, England. I am currently employed as a Professor in the Department of Pathology and Laboratory Medicine and as Director of General Chemistry at the University of Pennsylvania Medical Center. My employment history and fields of expertise are described in my curriculum vitae, attached as Exhibit A.

3. I have significant experience with both the design and the use of testing methods that rely on binding interactions between molecules to determine the presence, amount, and/or concentration of a particular substance in a sample of a solution. Such testing methods are commonly referred to as "binding assays." Over the years, I have published many papers and given numerous lectures on topics relating to binding assays, such topics including sample preparation, molecular binding interactions, the use of luminescence to detect binding, and the design and use of microarrays. In addition, I have been named as an inventor on a number of patents relating to binding assays and have been the recipient of several honors and awards for my work in the field. These publications, patents, and awards are summarized in Exhibit A.

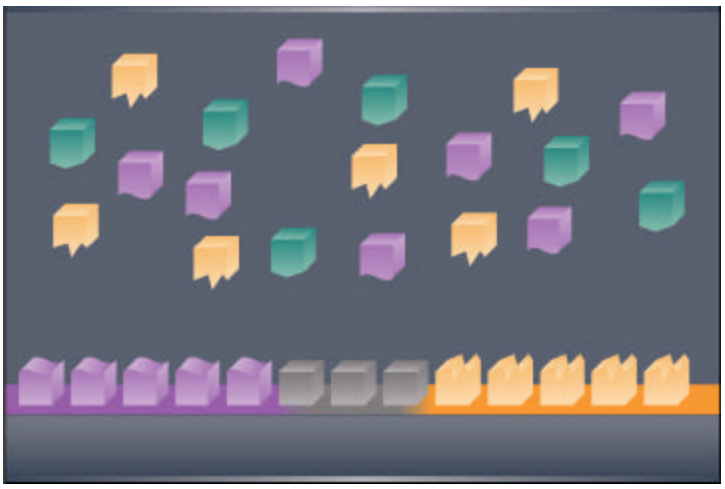
The Level of Ordinary Skill in the Art

4. A person of ordinary skill in the art of binding assays in the early to mid-1980's would have been a person with an undergraduate degree and approximately six to twelve months of professional experience in the field of biological sciences, such that the person had gained familiarity with the use of binding assays and the theory behind such assays.

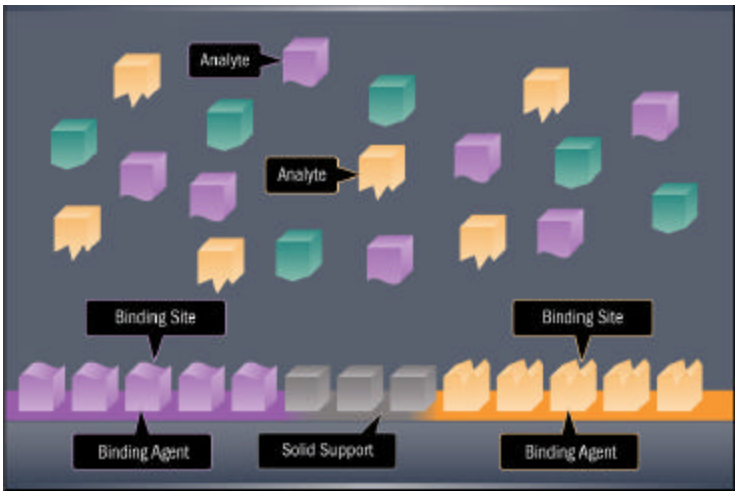
Binding Assays

5. In order to perform a binding assay, a sample of the solution of interest is contacted

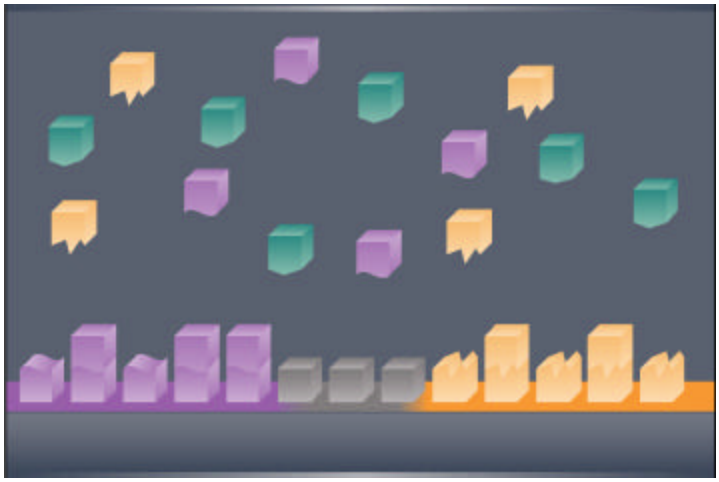
with a molecular substance—called a "binding agent"—that is capable of binding to the substance of interest in the solution. A simplified representation of a situation in which two different binding agents are attached to a solid support and are being used to test for two different substances (or "analytes") in the solution is depicted below:



6. In this case, the purple binding agent molecules are being used to detect the purple analyte molecules, and the orange binding agent molecules are being used to detect the orange analyte molecules. The green molecules represent another substance present in the sample that is not an analyte (because it is not being measured or detected). The green molecules will not bind to either the purple or the orange binding agent. The places at which the analyte molecules attach to the binding agent molecules are referred to as "binding sites," as shown below:



7. The binding between the binding agent molecules and the analyte molecules is "reversible," which means that the molecules can become unbound again after they have bound. What this means for the test system is that analyte molecules are continuing to bind to and to disassociate from the binding agent all the time, so that at any given moment, a different set of analyte molecules may be bound to the binding agent. If the system is allowed to settle to equilibrium, however, the total *number* of analyte molecules that are bound will stay the same (even though it might be different molecules that are bound from one moment to the next). As shown below, the reversible nature of the binding often means that not all of the binding sites are bound by an analyte molecule:



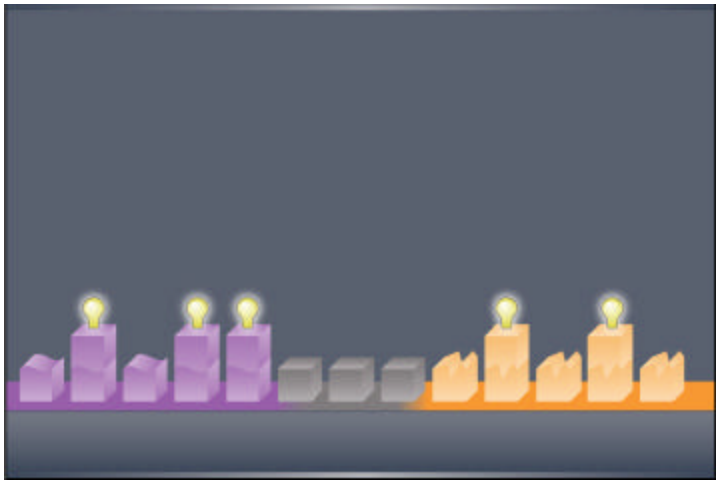
8. For every reversible binding reaction between two substances, there is a parameter, often known as the equilibrium constant, affinity constant, binding constant, or "K" value, that reflects how likely the two substances are to bind together compared to how likely they are to disassociate. Therefore, the affinity constant provides a measure of how much analyte in the system will be bound as compared to the amount unbound.

9. After the analyte has been allowed to bind with its corresponding binding agent, the support, with the bound analyte attached, is removed from the solution. The next step is to determine how much of the analyte has been captured by the binding agent during the test. However, because the analyte and binding agent themselves are very small and therefore not readily detected, even with highly sophisticated instrumentation, it is usual to use some type of chemical

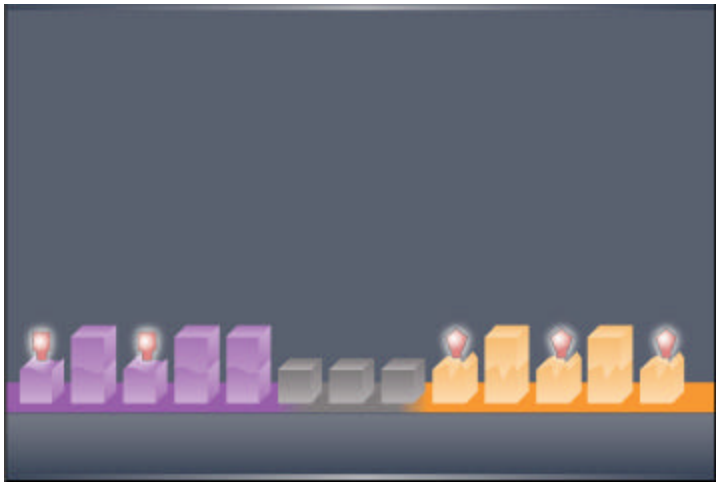
(or "reagent") that can be detected by a scanner or other similar instrument. These reagents can be detected by the instrumentation because they are labeled with substances with special properties, such as luminescence or radioactivity.

10. The reagents that are used to show how much analyte has been captured by the binding agent can work in one of two ways: (1) they can be bound to the analyte that has been captured by the binding agent, thus indicating the "filled" binding sites, or (2) they can be bound to the binding agent molecules that did not capture an analyte, thus indicating the "unfilled" binding sites. A simplified representation of these two alternative scenarios is depicted below:

Indication of "Filled" Sites



Indication of "Unfilled" Sites



11. Regardless of whether the detection reagent shows up the filled or the unfilled binding sites, the result will be to indicate the proportion of binding sites that have been taken up by analyte (either directly, in the case of detection reagents that show the "filled" sites, or by negative inference, in the case of detection reagents that show the "unfilled" sites).

12. Particularly in the case of detection reagents that are used to show the filled sites (as shown in the top graphic, above), the same detection reagent can be used for each binding agent on the support, provided that the different binding agents are in different, known locations on the support. For example, in the case of the top graphic, above, the same detection reagent can be used to detect the filled sites on the purple binding agent as is used to detect the filled sites on the orange binding agent. The result in that case will be no different from the result that would be obtained if one detection reagent were used for the purple binding agent and a different detection reagent were used for the orange binding agent.[1]

13. The basic idea that underlies many binding assays is that the proportion of binding sites that is filled by analyte will be related to the analyte concentration in the sample. Therefore, once a reagent is used to detect either the filled or the unfilled sites, the concentration of analyte can often be determined. One way to do this is to compare the test results with the results obtained from a series of "standards"—that is, samples of known concentrations of analyte.

14. Traditionally, binding assay methods involved the contacting of a precise, pre-measured volume of solution with a relatively large amount of binding agent. The amount of binding agent was "relatively large" in the sense that it was designed to bind a large proportion of the analyte of interest—often as much as, or more than, 50% of the analyte in the solution.

15. Because these conventional assay techniques captured so much of the analyte present in the solution, the overall concentration of analyte in the solution was greatly diminished, altering the very value that was to be measured. The proportion of bound sites depended, therefore,

[1] By contrast, in the case of detection reagents that are used to show the *unfilled* sites (as shown in the bottom graphic, above), it may be necessary to use different detection reagents for the different binding agents on the support. This is simply because it may not be possible to find one detection reagent with the ability to bind to all of the different unfilled binding agents.

on the volume of the sample. One had to control accurately the volume of the sample and of the standard solutions, such that an accurate comparison of the proportion of filled binding sites in the sample and in the standard solutions could be made.

16. The patents of Dr. Ekins that are at issue in this lawsuit describe a method of performing binding assays that differs significantly from the methods that were traditionally used. In particular, the patents recommend the use of very small amounts of binding agent—much less than had been used in traditional binding assays. The patents explain that the use of these small amounts of binding agent is advantageous in that it allows a measurement of an analyte to be made without significantly disturbing the system in the process of making the measurement. In particular, the patents liken the disclosed system to the use of a thermometer to measure the temperature in a room—the thermometer necessarily extracts some heat from the room, thus lowering the temperature, but the thermometer is small enough that the effect on the temperature is negligible. *See* '720 patent at col. 2, lines 47-60.

17. Because the systems disclosed in the patents in suit have the advantage of causing only an insignificant disturbance in the sample being measured, they also obviate the need to measure with accuracy the volume of sample being tested. This is because, even over large variations in volume, the very small amount of binding agent will capture the same number of analyte molecules for a given analyte concentration.

18. In addition, Dr. Ekins discovered that the use of very small amounts of binding agent led to heightened sensitivity as well as greater accuracy of results. *See, e.g.*, '099 patent at col. 3, lines 3-18. These discoveries allowed for the development of miniaturized testing methods that could test for numerous different analytes using different binding agents attached to the same solid support—systems commonly referred to as "microarrays."

Binding Agents

19. "Binding agent" is a term used in the art of binding assays to refer to molecules that have sites that bind to other substances. It is broad, generic term, and it is used to refer to a wide range of different types of molecules, including proteins, antibodies (which are specialized types of proteins), and nucleic acids. "Binding agent" is also considered synonymous in the art with several other similar terms, including "binding reagent," "binding substance," and "binder."

20. For example, in my treatise on "Ligand-Binder Assays," published in 1985, a true and correct copy of which is attached hereto as Exhibit B, I explained that a "binder" is "any molecule which exhibits molecular recognition for another molecule (ligand)" and then went on to list a number of different "binders," including DNA. *See* Ex. B at 7.

21. Similarly, in a 1988 book chapter that I authored, entitled "Molecular and ionic recognition by biological systems," a true and correct copy of which is attached hereto as Exhibit C, I discussed the characteristics of several different binding agents, again including DNA.

22. The concepts discussed in the patents in suit are applicable to all of the types of binding reactions discussed in Exhibits B and C, including the binding of the two strands of a segment of a DNA molecule. In particular, the binding between two strands of DNA is governed by an affinity constant, or "K" value. When two strands of DNA bind together, as with other binding reactions, the binding is reversible, meaning that the two strands can separate. The affinity constant is a measure of how much of the substance is bound and how much is unbound at any given time. I explicitly recognized in Exhibit B that DNA binding reactions are governed by an affinity constant: "Other binders include . . . DNA (Ranki et al., 1983). An important property of a binder is its equilibrium binding constant (K) . . . ." Ex. B at 7.

23. In addition, DNA molecules that are used as binding agents can be attached to a solid support for use in binding assays. Again, I noted this explicitly in Exhibit B: "If a binder can be rendered insoluble by attachment to an insoluble material (a solid support, matrix, or carrier), and if this immobilized binder retains a substantial amount of its binding properties, then it may replace soluble binder in a binding assay. . . . [O]ther binders such as protein A . . ., DNA, cell receptors, a substrate . . ., and a fragment of the first component of complement, Clq . . ., have been

used in an immobilized form." Ex. B at 76-77.

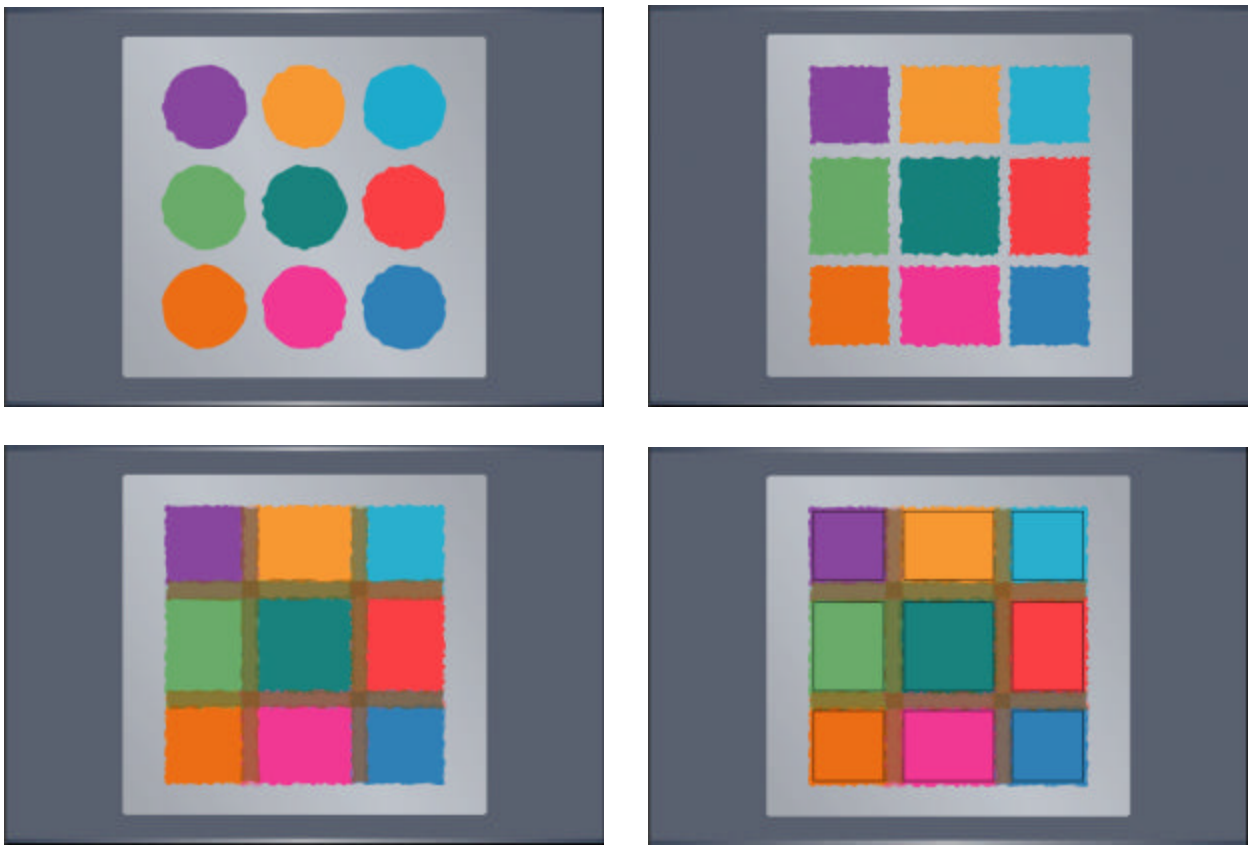
24. I have reviewed U.S. Patent No. 4,299,916, a true and correct copy of which is attached hereto as Exhibit D. The word "immunoassay," which is used in the title and throughout the '916 patent is a word that implies the use of an antibody. Nonetheless, the '916 patent recognizes that the binding processes that are discussed in the patent are equally applicable to nucleic acids. *See* Ex. D at col. 5, lines 1-7; col. 16, lines 49-53.

Spots of Binding Agent

25. When different binding agents are applied to a solid support in "spots," the primary purpose of each of the spots is to provide a signal, by means of an appropriate detection reagent, indicative of the amount of analyte bound to the spot. The signals generated by the spots are intended to be reflective of the binding of an analyte that the spot was designed to capture. Therefore, in order to provide a useful signal, the spot must contain a binding agent that is capable of binding, and is reasonably specific for, an analyte in the sample. What exists between the spots of different binding agents is unimportant, provided that useful signals can be obtained from the spots.

26. The '099 and '755 patents refer to the use of albumen "to saturate the residual binding sites in the wells." *See, e.g.*, '099 patent at col. 10, line 12; *see also id.* at col. 7, lines 32-37. In this context, albumen is being used to "fill in" places on the support that are not coated with binding agent that is specific for an analyte. Albumen is a protein that can bind to certain substances and that is therefore a type of binding agent.

27. The representation below demonstrates different arrangements of spots that would be capable of providing a useful signal from each spot. In the top two, there is only "empty" support material between the spots. In the bottom two, there exists between the spots some type of binding agent, but that binding agent is not designed to bind an analyte in the sample and so is not generating a useful signal. The black boundaries included in the last picture show the boundaries of the spots—that is, the areas from which the useful signals are obtained.



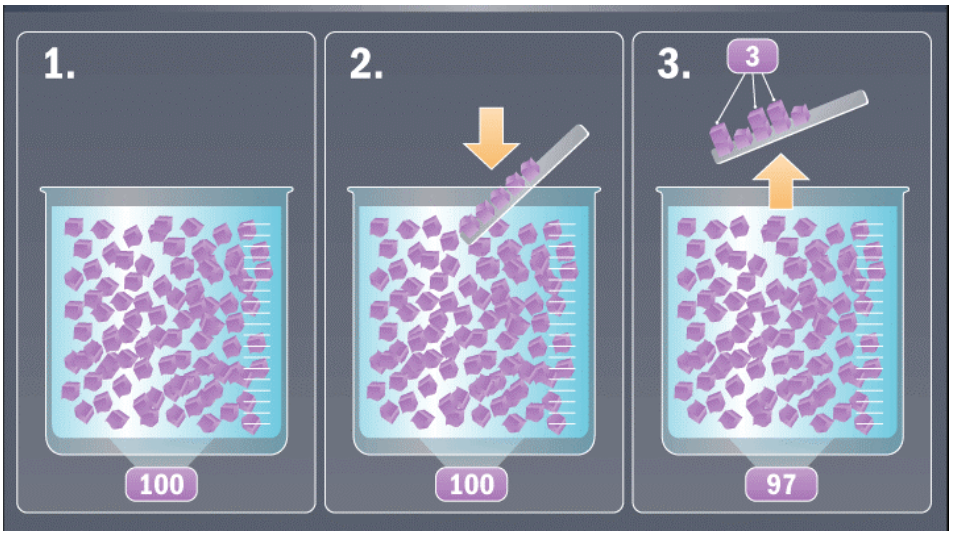
The Meaning of "Insignificant Effect" and "Small Amount"

28. The guidance provided in the specification of the '720 patent would have been sufficient to instruct one of ordinary skill in the art in the early to mid-1980's as to the meaning of "insignificant effect" and "small amount," as used in the patent claims. In particular, column 3, line 66 to column 4, line 16 of the specification explains the parameters that should be taken into account in determining what is an insignificant effect.

29. A person of ordinary skill in the art would understand that an effect that is

"insignificant" would be one that would not take the parameter being measured—in this case, the concentration of analyte—outside of the margin of error commonly associated with the test being performed. It is understood that tests have error ranges associated with them, and it would therefore not be a difficult matter for one of ordinary skill in the art to determine the scope of the "insignificant effect," as set forth in the patent, for a given test.

30. Shown below is a simplified depiction of the effect on the analyte concentration in a fluid of removing 3% of the analyte in the fluid—which of course is less than the 5% number that the '720 patent provides as an upper limit on the type of effect that will generally be considered to be insignificant, *see* '720 patent at col. 4, lines 13-16:



31. It would also not be a difficult matter for one of ordinary skill in the art to determine the amount of binding agent corresponding to the "small amount" described in the '720 patent. The claims of the patent themselves explain that a "small amount" of binding agent is an amount that has an insignificant effect on the analyte concentration, and, as explained above, one of ordinary skill would be able to determine the magnitude of an "insignificant effect." That person would then be able to determine—at least through straightforward trial and error, if not by other means—the amount of binding agent that would not cause more than an insignificant effect on the analyte concentration.

I declare under penalty of perjury pursuant to the laws of the United States that the

foregoing is true and correct. Executed this 9th day of April, 2004 in Devon, Pennsylvania.

s/ Larry J. Kricka
Larry J. Kricka

ECF CERTIFICATION

I, Michael K. Plimack, am the ECF User whose identification and password are being used to file this Declaration of Dr. Larry J. Kricka in Support of Multilyte Ltd.'s Opening Claim Construction Brief. In compliance with General Order 45.X.B, I hereby attest that Larry J. Kricka has concurred in this filing.

DATED: April 9, 2004

HELLER EHRMAN WHITE & McAULIFFE LLP

By s/ Michael K. Plimack

Attorneys for Defendant and Counterclaimant
MULTILYTE LTD.